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REMARKS

Claims 1-9, 12, and 13 are pending in the present application. By this Amendment, claims 10 and 11 are cancelled and claim 9 is amended to recite the limitations of cancelled claim 11. No new matter is added.

Entry of this Amendment is respectfully requested. In as much as the amendment serves to incorporate the limitations of a dependent claim into its parent claim, the amendment does not introduce any new issues or require any further consideration or search. Therefore, entry of this Amendment is appropriate.

§102(b) Rejection over Olondriz

Claims 9-11 and 13 are rejected under 35 U.S.C. §102(b) as being anticipated by Olondriz (ES 2050069 to Marquillas Olondriz et al.). This rejection is respectfully traversed.

Claim 9 presently recites that the amount of Z-isomer is at least 95% (based on the total amount of the enriched Z-isomer oxime of claim 9). It is the Office Action's position that in order for Olondriz to obtain the 84.7% yield in Example 10 (cols. 7-8 of Olondriz), "the Z-isomer must have been present in the oxime mixture in excess of 90%, since most cyclized reactions do not go to 100% yield." The Office Action has failed to meet its burden to provide a reasonable basis to support the determination that the alleged inherent amount of Z-isomer *necessarily* flows from the teachings of Olondriz.

First, as previously argued, the Office Action has failed to establish that it is necessary for the Z-isomer to have been present in excess of 84.7%, because as the Z-isomer is cyclized, the supply of Z-isomer may be replenished by conversion of E-isomer

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to Z-isomer. Thus, Olondriz's 84.7% yield does not *necessarily* require an initially high isomeric purity, as the Office Action contends, but could simply be the result of equilibrium forces surrounding the isomerisation and cyclization of the Z-isomer.

Second, even if the Office Action is correct that an amount of greater than 84.7% of Z-isomer is required to obtain Olondriz's 84.7% yield, the Office Action provides no reasonable basis for why an initial Z-isomer amount of at least 95% (e.g., as opposed to 85%, 88%, 90%, 92%, or even 94%, all of which are outside the scope of claim 9) is *necessarily* required. The fact that such reactions may not "go to 100% yield" does not explain or justify why at least 95% purity would be needed or even likely. In short, even assuming an initial Z-isomer purity of greater than 84.7% must have been present, why would a worker skilled in the art conclude that at least 95% purity was used? This is a factual gap in the Office Action's position. The Office Action provides no reasonable basis in scientific fact or technical reasoning why an initial Z-isomer amount of at least 95% is necessary or likely.

For at least these reasons, Olondriz does not inherently teach the claimed amount of Z-isomer, and Olondriz thus does not anticipate claims 9 and 13. Withdrawal of this rejection is respectfully requested.

§102(b) Rejection over Kennis

Claims 9-12 are rejected under 35 U.S.C. §102(b) over Kennis (U.S. Patent No. 4,804,663 to Kennis et al.). As suggested by the Office Action, attached hereto is a Declaration under 37 C.F.R. §1.132 of Martin Dobsik showing that Experiment 1 of Kennis (cols. 10-11 of Kennis) was repeated and resulted in an oxime hydrochloride salt – not an enriched Z-isomer oxime free base as recited in claims 9 and 12. Applicants

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note that the Declaration refers to "Example 1 of EP 196,132." EP 196,132 corresponds to Kennis, and Example 1 of EP 196,132 is identical to Experiment 1 of Kennis.

Inasmuch as the Declaration was requested by the 7/14/06 Office Action, and the data in the Declaration was presented to the Office Action in the 1/17/07 Amendment and already considered by the Examiner, entry of this Declaration after a final rejection is appropriate.

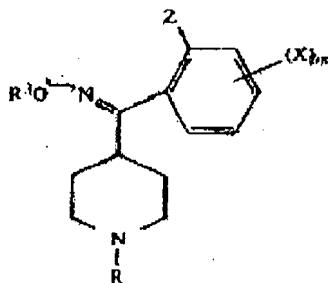
Applicants point out that minor errors were present in the previously presented data that was included, in unverified form, in the 1/17/07 Amendment. Some of the "Mother Liquor" percentages were incorrect (e.g., in Experiment 1 the E and Z Mother Liquors did not sum to 100% and the remaining amount of starting ketone in each Mother Liquor was misstated). Also, the yield in Experiment 2 was reported as 8.16 parts but really is 8.46 parts. These minor inconsistencies are due to an inadvertent error in communicating the data from the declarant to Applicants' representative in the preparation of the Amendment filed 1/16/07. Inasmuch as the data concerning the solid product is the same, these minor corrections do not alter the merits of Applicants' traversal of the §102(b) rejection over Kennis. That is, Kennis' Experiment 1 resulted in an oxime hydrochloride salt and not an enriched Z-isomer oxime free base, as per the instant claims. As acknowledged in the Office Action, the submission of this data in a Declaration is sufficient to overcome this §102(b) rejection over Kennis. Accordingly, withdrawal of this rejection is respectfully requested.

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§103(a) Rejection over Strupczewski

Claims 1-8 are rejected under 35 U.S.C. §103(a) as being obvious over Strupczewski (U.S. Patent No. 4,408,054 to Strupczewski et al.). This rejection is respectfully traversed.

Strupczewski teaches a compound of the general formula



and salts thereof (see claim 1 of Strupczewski) as an intermediate in the formation of 3-(4-piperidyl)-1,2-benzisoxazoles. There are no limitations on the "salts thereof," e.g., there is no requirement for the salt to be a pharmaceutically-acceptable salt or even an acid addition salt. Example 25 of Strupczewski discloses 4-(2,4-difluorobenzoyl)-piperidine oxime, which is encompassed by the generic formula. The Office Action indicates that it would have been obvious to make a salt of the oxime of Example 25 based on claim 1 of Strupczewski. The Office Action goes too far, however, by asserting that it would have been obvious to make the acetic acid salt of the oxime of Example 25.

Referring to col. 10 of Strupczewski, the Office Action indicates that it would have been obvious to specifically make the acetic acid salt of the oxime of Example 25 because "acetic acid" is listed among the pharmaceutically acceptable salts at lines 61-68.

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The Office Action refers to the disclosure at lines 61-68 as "a global teaching of pharmaceutically acceptable salts." The Office Action's analysis is flawed.

First, the Office Action takes the disclosure at lines 61-68 out of context. Col. 10, lines 55-68, reads as follows:

...The 3-(4-piperidyl)-1,2-benzisoxazoles of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience or crystallization, increased solubility and the like.

Preferred pharmaceutically acceptable addition salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid and the like, salts of monobasic carboxylic acids such as, for example, acetic acid, propionic acid and the like, salts of dibasic carboxylic acids such as, for example, maleic acid, fumaric acid and the like, and salts of tribasic carboxylic acids such as, for example, carboxysuccinic acid, citric acid and the like.

(emphasis added). Clearly, this portion of col. 10 is describing pharmaceutically acceptable salts of the 3-(4-piperidyl)-1,2-benzisoxazole final product. It is not a global teaching of using pharmaceutically acceptable salts for each of the intermediates used to make the benzisoxazole final product. A worker skilled in the art would not have been motivated to select a preferred 3-(4-piperidyl)-1,2-benzisoxazoles pharmaceutically acceptable salt for use with the intermediate oxime of Example 25, particular where Strupczewski's claim 1 does not limit the "salt thereof" to being a pharmaceutically acceptable salt or even an acid addition salt.

Second, the Office Action has provided no rationale for why the skilled worker would have been motivated to specifically select a monobasic carboxylic acid salt as opposed to a mineral acid salt (such as a salt of "hydrochloric acid, sulfuric acid, nitric acid, and the like"), a dibasic carboxylic acid salt (such as a salt of "maleic acid, fumaric

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acid, and the like"), or a tribasic carboxylic acid salt (such as a salt of "carboxysuccinic acid, citric acid, and the like") all of which are described at col. 10, lines 61-68.

Furthermore, the Office Action has provided no rationale for why the skilled worker would have been motivated to specifically select acetic acid as the monobasic carboxylic acid, for example, as opposed to propionic acid (line 65), formic acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, lauric acid, or stearic acid.

Third, a skilled worker would not have been motivated to make an acetic acid salt of the oxime intermediate of Strupczewski's Example 25, because Strupczewski does not teach or suggest that an acetic acid salt of the oxime intermediate has any desirable properties as compared to the free base or other salts thereof. For example, Strupczewski does not teach or suggest that making the oxime intermediate into an acetic acid salt provides any benefits or advantages during the formation of 3-(4-piperidyl)-1,2-benzisoxazoles. Indeed, Example 25 does not convert the oxime to any salt, much less the acetic acid salt. Neither does Strupczewski teach or suggest that "the Z and E isomer oxime can be readily separated from one another when converted into an acetic acid salt form," or that "[t]he oxime(s) can be isomerically enriched by [sic] the use of the novel acetic acid salt thereof, which affords, *inter alia*, resolution of the isomers and/or by heat conversion," as described in the present specification at p. 6, lines 9-13, and the abstract. Because Strupczewski does not teach or suggest the desirability of an acetic acid salt of the oxime intermediate of Example 25, a worker of ordinary skilled in the art would not have been motivated to make it.

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Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness over Strupczewski, and Strupczewski thus does not render claims 1-8 obvious. Withdrawal of this rejection is respectfully requested.

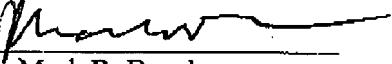
Conclusion

In view of the above amendments and remarks, the presently-claimed subject matter is novel and unobvious over the applied prior art. Reconsideration and withdrawal of the rejections and allowance of the present application are respectfully requested.

Should the Examiner have any questions regarding this application, she is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,

Date: September 4, 2007
(Tuesday after Federal Holiday)

By: 

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Attachments:

Rule 132 Declaration of Martin Dobsik (executed)
Petition for Extension of Time
Notice of Appeal

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